Available online at https://asric.africa/health-sciences
ASRIC Journal of Health Sciences Vol.5(1)(2025) 58-72

Association of FSH with High-Density Lipoprotein In Postmenopausal Periods: A Systematic Review and Meta-Analysis

Yonatan Kindie[1], Getnet Fetene[2], Abebaw Worede[2], Mastewal Yechale[1]

[1]MSc in clinical chemistry, Debre Markos university, Debre Markos Ethiopia, email-yonatankindie1213@gmail.com, mastewalyechale13@gmail.com

[2]Clinical Chemistry, university of Gondar, Gondar, Ethiopia, email-getnetfetene44@gmail.com), email-woredeabebaw@yahoo.com)

Corresponding author: yonatankindie1213@gmail.com

Received 29 June 2025; revised 14 August 2025; accepted 29 September 2025

Abstract

Prior researchers identified a number of studies on the metabolism of lipids among postmenopausal women. Though more recent studies have demonstrated that FSH has extragonadal effects on HDL, they still connected it to the amount of estrogen. Follicle-stimulating hormone (FSH) has been proposed as a potential determinant of lipid changes after menopause, but the evidence is inconsistent. **Objective:** To examine the association between FSH and high-density lipoprotein cholesterol (HDL-C) among post-menopausal women. We systematically searched PubMed, Scopus, Web of Science and Embase for studies published up to 15 August 2024. Eligible studies reported quantitative associations between circulating FSH and HDL-C in post-menopausal women. Random-effects meta-analysis pooled correlation coefficients; β-coefficients were transformed to r using the formula $r = (\beta \times sX) / sY$. Heterogeneity and small-study effects were assessed with the Q-test, I^2, Galbraith plots, Egger's regression and trim-and-fill adjustment. Meta-regression and subgroup analysis were employed to find possible modifiers for the overall correlation coefficient. Twelve studies (eleven cross-sectional studies and one prospective cohort) were included in this systematic review and meta-analysis. The pooled correlation coefficient between FSH and HDL was positive ($r = 0.31$; 95 % CI 0.09–0.53; $p = 0.006$), indicating a moderate positive relationship. Between-study heterogeneity was substantial ($I^2 = 100$ %, $p < 0.001$). Egger's test suggested possible small-study effects, but trim-and-fill correction produced a similar estimate Higher FSH levels are moderately associated with higher HDL-C in post-menopausal women; however, the association is variable across studies and should be interpreted cautiously given extreme heterogeneity, residual confounding and predominance of cross-sectional designs. Further high-quality prospective studies are needed to clarify causality and clinical utility.

Keywords: Postmenopausal; Association; Correlation; HDL; Estrogen

Introduction

Female sex hormones affect the health of women at every stage of their lives. In women going through the menopausal transition, ovarian degeneration results in notable changes in sex hormones. Adipose tissue accumulation is accompanied by a sharp increase in FSH and a sharp decline in estradiol levels (Liu et al., 2023). Triglycerides, total cholesterol, and low-density lipoprotein levels will all rise as a result, and high-density lipoprotein levels will decrease, among other CVD risk factors. Although many of the physiological changes associated with menopause have been linked to the decrease in estrogen levels, there is mounting evidence that suggests FSH may have an independent effect on the risk of lipid profile alteration. (Serviente et al., 2019).

Prior research on postmenopausal women has looked at the relationship between HDL and estrogen (Wenger, 2002; Litwak et al., 2014; Mauvais-Jarvis et al., 2017). Some studies focus on the increase in FSH during the menopausal transition in addition to the impact of estrogen. As the number of primordial follicles gets closer to zero, the ovaries produce less estrogen. The production of gonadotropins can no longer be inhibited by estrogens when it drops below a critical level (Obeagu & Obeagu, 2016) and Serum levels of FSH increased from 15.15 to 98.21 mIU/ml(Randolph et al., 2011).

In physiology, FSH activates the Ca2+ channel by binding to an inhibitory G protein subunit coupled FSH-receptor. Through the activation of the Cyclic AMP Response Element-Binding Protein pathway and the phosphorylation of Protein Tyrosine Phosphatase, Non-Receptor Type 5, intracellular calcium influx facilitates the production of lipids and helps gonadotropin-releasing hormone to promote the secretion of FSH. In the presence of β-arrestin, phosphorylated protein kinase B is activated when FSH binds to an inhibitory G protein subunit-coupled FSH receptor. It increases the transcription of the genes for 3-Hydroxy-3-Methylglutaryl-CoA Reductase and Sterol Regulatory Element-Binding Protein 2 to produce cholesterol by blocking Fork head Box O1 (Mao et al., 2022).

It was widely accepted until recently that postmenopausal women had a significantly higher risk of CVD, with the decline in estrogen levels being a major contributing factor (El Khoudary et al., 2012).

It's interesting to note that studies on Chinese postmenopausal women have shown a correlation between serum TC and LDL-c and FSH levels. According to certain research, a higher chance of HDL reduction was linked to an increase in FSH (Chu et al., 2003; Song et al., 2016).While others had shown higher FSH levels are related with lower risk(Wang et al., 2017; Bertone-Johnson et al., 2017 & 2018). Irrespective of the direction of the association, there is emerging evidence that shows the relationship between FSH and HDL levels(Chu et al., 2003; Song et al., 2016). Studies on the impact of FSH on postmenopausal women's lipid profiles have produced mixed results, and it is unclear how FSH influences the development and progression of CVD risk factors. Because the relationship between circulating follicle stimulation and cardiometabolic risk factors, such as lipids, in postmenopausal women is less well understood, this systematic review and meta-analysis will investigate it. For this reason, a thorough literature review is desirable.

Methods

Searching strategy: A review of the literature was conducted using Cochran Library, PubMed, Plose, Google Scholar, and Scopus. Only English-language publications involving human subjects were included in the search. Every study released up until August 15, 2024, was taken into account. A flow chart of Preferred Reporting Items for Systematic Reviews and Meta analyses (PRISMA) was used to select the studies. Using this supposition, the following search terms and Boolean operators were used to find studies from PubMed: ((Gonadotropins [Title/Abstract]) OR (Follicle stimulating hormone [Title/Abstract])) AND (lipid profiles[Title/Abstract])) OR (Dyslipidemia [Title/Abstract])) OR (hypercholesterolemia [Title/Abstract])) (hypertriglyceridemia [Title/Abstract])) OR (hyperlipidemia [Title/Abstract]))) OR(CVD[Title/Abstract])))) AND (postmenopausal women [Title/Abstract])). A total of 763 papers were found in PubMed, and after screening, 47 papers were left over and saved to Endnote 21.

Eligibility Criteria

Inclusion Criteria

Research papers that demonstrate the relationship, impact, role, and influence of gonadal and follicle-stimulating hormones on the rise or fall in HDL concentrations, as well as studies that included postmenopausal women as study participants, must be published in English and meet the following requirements: Publications that reported the effect of follicle stimulating hormone on the correlation or beta coefficient of HDL-C levels were included, as were original studies involving healthy postmenopausal women.

Exclusion Criteria

Studies that included postmenopausal women with lipid-altering diseases like diabetes, coronary artery disease, cancer, and thyroid functional abnormalities, studies that included postmenopausal women who received hormone replacement therapy (HRT) or other medications that will affect lipid metabolism, studies that did not include information such as author, year, country, sample size, or study design, and studies that reported the mean level of lipids but did not state the degree of association in terms of correlation coefficient or beta-coefficient to be estimated to correlation coefficient were also excluded.

Data Extraction

We extracted and summarized data from the included research. It was anticipated that the publications that would be included in this meta-analysis would report the total number of postmenopausal subjects as well as the association, correlation, effect, or role of FSH on the concentration or mean value of HDL among the postmenopausal women in the form of a Pearson correlation coefficient.

When multiple publications reported the same or comparable findings, we considered the most recent study with the largest sample size. The first author, year, nation, study design, sample sizes of the study groups, and the connection between FSH and HDL-C were all taken out of each qualifying study using Microsoft Excel. The 2020 PRISMA guidelines were closely adhered to during the review process. Figure 1 presents the flow diagram in a transparent manner.

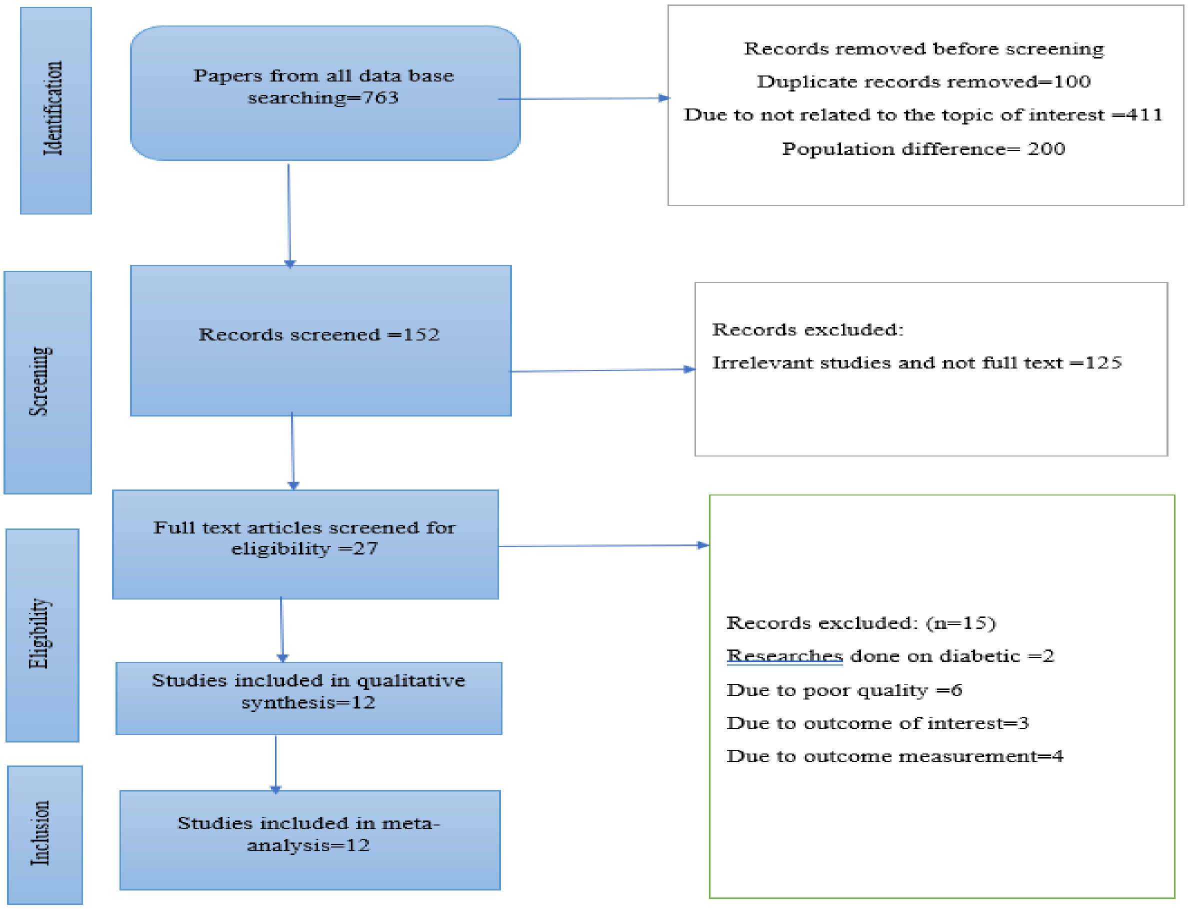


Fig. 1*:PRISMA flow diagram*

Assessment of Methodological Quality

The modified Newcastle OTTAWA Quality Assessment Scale, a method for evaluating the quality of articles for cross-sectional studies, was used to evaluate the papers' quality. Seven criteria were used to evaluate these cross-sectional studies. The sample's representativeness (*), size (*), rate of non-respondents (*), and exposure (risk factor) determination (**, *), Comparability of participants in various result groups according to the analysis or study design (*), Evaluation of the results (**, *) and the statistical test used to the analysis (*) (Herzog et al., 2013). One star represents value number 1 and two star indicates value number two given for each of the quality criteria.

Data Processing and Analysis

After data was extracted from relevant studies, STATA version 17 was used to compile and evaluate the data. The random-effects model for predicting the between-study variance was used to determine the overall pooled effect size, which is the correlation coefficient for each component of the lipid profile. Since the fixed-effect model is known to favor larger studies, it assigns these studies higher weights and presumes that sampling error is the only cause of the variation in effect sizes.

The random-effects model, on the other hand, makes the assumption that sampling error and population variability in effect sizes are the causes of the variability in effect sizes and aims to more uniformly distribute the weights across small and big studies. Theta, or the pooled correlation coefficient, was used to summarize the findings of the FSH connection with HDL in tables and graphs. A forest plot was used to graphically represent the correlation coefficient and the overall estimated effect size.

To evaluate the variation across the included studies and demonstrate the impact of FSH on HDL, the Galbraith test of heterogeneity was employed. The existence of minor study effects on the overall correlation coefficient was indicated using Egger's test. To pinpoint the precise moderator or predictor causing the overestimation of the pooled effect size, meta regression was used. Subgroup analysis was performed once more for studies exhibiting significant heterogeneity. Lastly, by altering the model and excluding and including specific studies, sensitivity analysis was performed on each pooled effect size.

Results

Characterstics of the Included Studies

Following a thorough and methodical search of the literature, 763 papers in total were found. 27 papers were selected for full-text evaluation after being vetted by title and abstract after duplicates and irrelevant research were eliminated. It was determined that 12 of these full-text screened publications, which included 8947 research participants, qualified for this meta-analysis.

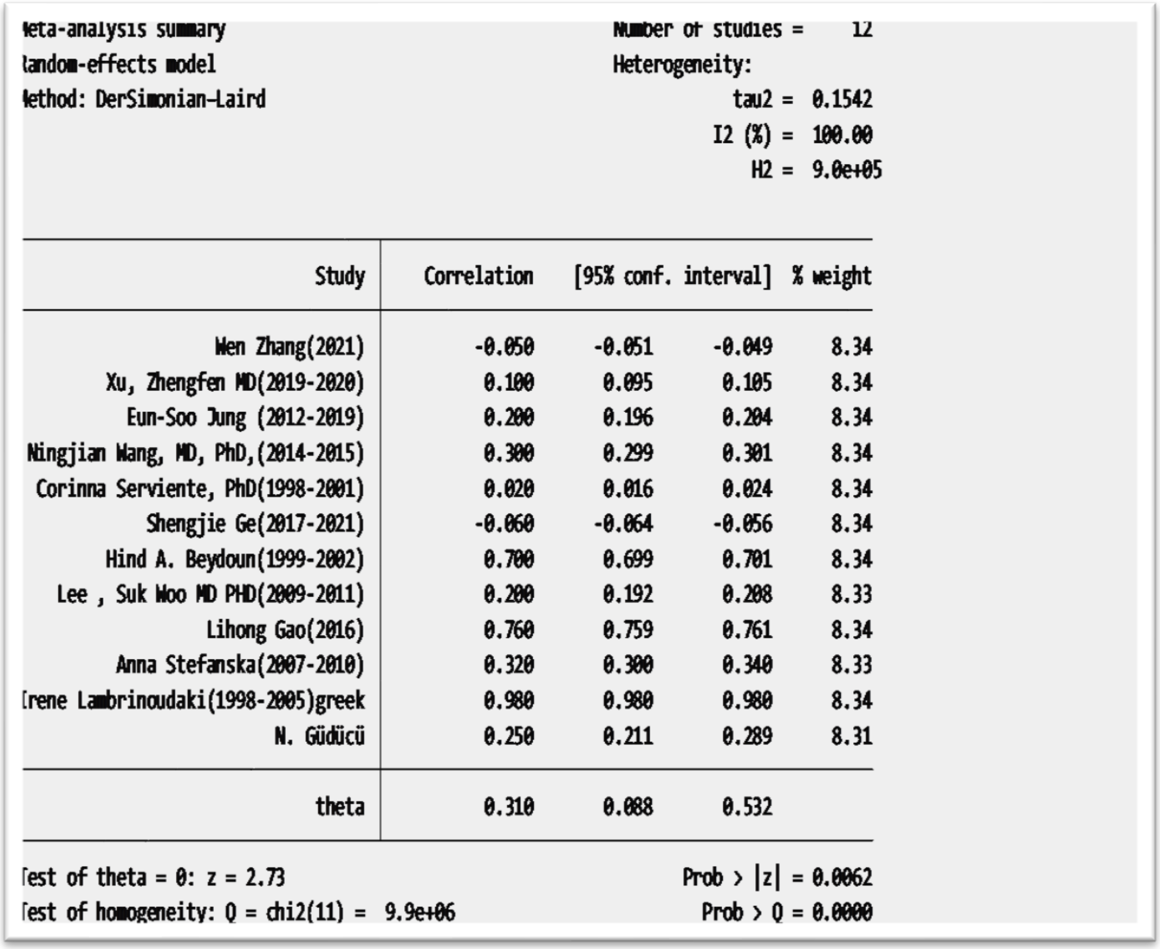
Research papers conducted worldwide between 1998 and 2024 that reported either or both the correlation coefficient and beta coefficient were included in this meta-analysis. Studies that reported the correlation coefficient were used directly, while those that reported only the beta coefficient were calculated and analyzed using the estimated correlation coefficient. For this purpose, for simple regression with standardized variables, the value of beta coefficient and correlation coefficient were considered as equal. For simple regression with unstandardized variables r=standard deviation of the predictor variable “x” divided by standard deviation of the outcome variable “y” when standard deviations were available. However standardized multiple regression tables were not considered because we cannot get a correlation coefficient from a single β without either the full predictor correlation matrix or additional regression statistics such as R-squared and partial/semi partial correlations.

The quality of eligible studies was evaluated using a modified version of the "Newcastle Ottawa" scaling technique.

Meta-Analysis Summary of HDL

The summary data was created using the random effect model. The correlation coefficient, either overall or pooled, was 0.31 [95% CI:0.088,0.532]. This indicates that, out of the twelve studies that were done to demonstrate the relationship between FSH and lipid profiles in postmenopausal women, the rise in FSH levels during this time is positively connected with HDL concentrations and statistically significant (p-value = 0.0062, less than 0.05).

According to the heterogeneity statistics presented in I 2(%), there is significant heterogeneity and 100% of the variation in effect size estimates may be attributed to differences between studies. As seen in figure two below, the Q test statistic with a p-value of < 0.001 indicates that there is high heterogeneity among the individual studies.



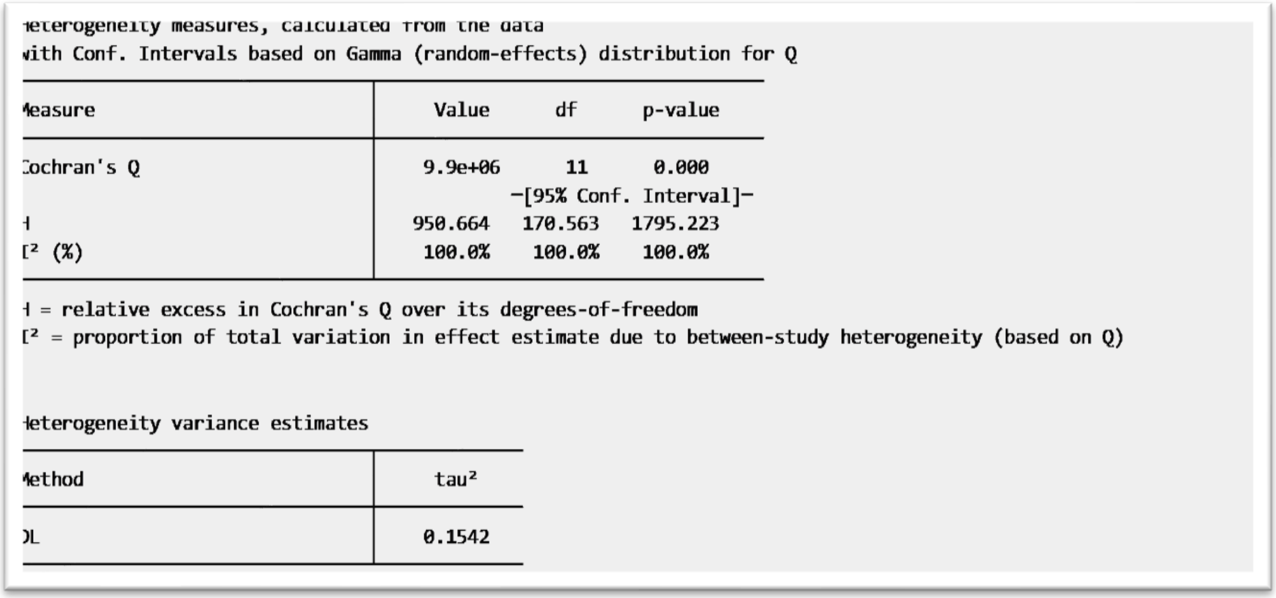
```
eta-analysis summary                               Number of studies =     12
andom-effects model                                Heterogeneity:
ethod: DerSimonian-Laird                                       tau2 =  0.1542
                                                             I2 (%) =  100.00
                                                                 H2 = 9.0e+05

--------------------------------------------------------------------------
                             Study |   Correlation   [95% conf. interval]  % weight
-----------------------------------+--------------------------------------
                   Wen Zhang(2021) |      -0.050     -0.051     -0.049      8.34
      Xu, Zhengfen MD(2019-2020)   |       0.100      0.095      0.105      8.34
        Eun-Soo Jung (2012-2019)   |       0.200      0.196      0.204      8.34
Ningjian Wang, MD, PhD,(2014-2015) |       0.300      0.299      0.301      8.34
 Corinna Serviente, PhD(1998-2001) |       0.020      0.016      0.024      8.34
           Shengjie Ge(2017-2021)  |      -0.060     -0.064     -0.056      8.34
       Hind A. Beydoun(1999-2002)  |       0.700      0.699      0.701      8.34
   Lee , Suk Woo MD PHD(2009-2011) |       0.200      0.192      0.208      8.33
                  Lihong Gao(2016) |       0.760      0.759      0.761      8.34
        Anna Stefanska(2007-2010)  |       0.320      0.300      0.340      8.33
rene Lambrinoudaki(1998-2005)greek |       0.980      0.980      0.980      8.34
                        N. Güdücü  |       0.250      0.211      0.289      8.31
-----------------------------------+--------------------------------------
                             theta |       0.310      0.088      0.532
--------------------------------------------------------------------------
est of theta = 0: z = 2.73                               Prob > |z| = 0.0062
est of homogeneity: Q = chi2(11) =  9.9e+06               Prob > Q = 0.0000
```

Fig 2: *meta-analysis summary of HDL among studies included in this metanalysis*

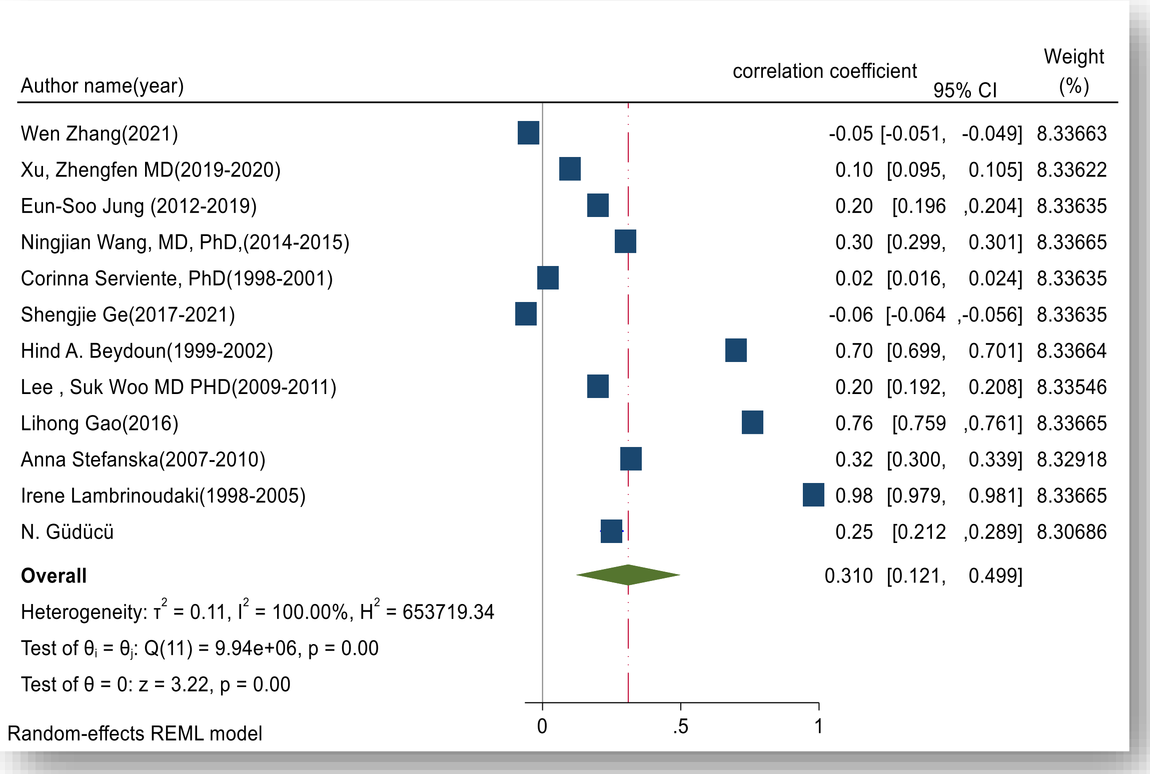
Forest Plot of FSH Effect on HDL

There is statistically significant heterogeneity among the studies due to the Cochran's Q significant p-value of 0.000 in table one is less than 0.05 implies the heterogeneity is greater than expected by chance. When Cochran's Q reveals significant heterogeneity, it may be necessary to investigate possible sources of variability using subgroup analysis or meta-regression.

Table 1: table of forest plot summary



```
eterogeneity measures, calculated from the data
ith Conf. Intervals based on Gamma (random-effects) distribution for Q

easure                       Value       df       p-value

ochran's Q                 9.9e+06       11        0.000
                                  -[95% Conf. Interval]-
                           950.664    170.563   1795.223
² (%)                       100.0%     100.0%     100.0%

 = relative excess in Cochran's Q over its degrees-of-freedom
² = proportion of total variation in effect estimate due to between-study heterogeneity (based on Q)


eterogeneity variance estimates

ethod                        tau²

L                           0.1542
```



Author name(year)	correlation coefficient	95% CI		Weight (%)
Wen Zhang(2021)	-0.05	[-0.051,	-0.049]	8.33663
Xu, Zhengfen MD(2019-2020)	0.10	[0.095,	0.105]	8.33622
Eun-Soo Jung (2012-2019)	0.20	[0.196	,0.204]	8.33635
Ningjian Wang, MD, PhD,(2014-2015)	0.30	[0.299,	0.301]	8.33665
Corinna Serviente, PhD(1998-2001)	0.02	[0.016,	0.024]	8.33635
Shengjie Ge(2017-2021)	-0.06	[-0.064	,-0.056]	8.33635
Hind A. Beydoun(1999-2002)	0.70	[0.699,	0.701]	8.33664
Lee , Suk Woo MD PHD(2009-2011)	0.20	[0.192,	0.208]	8.33546
Lihong Gao(2016)	0.76	[0.759	,0.761]	8.33665
Anna Stefanska(2007-2010)	0.32	[0.300,	0.339]	8.32918
Irene Lambrinoudaki(1998-2005)	0.98	[0.979,	0.981]	8.33665
N. Güdücü	0.25	[0.212	,0.289]	8.30686
Overall	0.310	[0.121,	0.499]	

Heterogeneity: τ^2 = 0.11, I^2 = 100.00%, H^2 = 653719.34

Test of $\theta_i = \theta_j$: Q(11) = 9.94e+06, p = 0.00

Test of θ = 0: z = 3.22, p = 0.00

Random-effects REML model

Fig. 3:diagrammatic representation of forest plot

In the graph displayed in Figure 3, every box corresponds to a study. The size of the box (area) is proportional to the study's weight, and its midpoint represents the point estimate of the effect size (correlation). The horizontal line within the box indicates the 95% confidence interval (CI) for the study's estimate. The pooled results are not evenly influenced by each study. Studies with a higher sample size generally offer more information and are therefore given more weight. The total pooled effect from the included studies is shown by the diamond beneath the studies. The width of the diamond shows the confidence interval for the overall effect. In addition to this, the forest plot contains the vertical line, the line of 'no effect', which corresponds to the value of zero in this meta-analysis, as the outcome is continuous, 0.001< 0.05 & < 0.1 indicates statistically significant between-study heterogeneity.

Heterogeneity Assessment

The Galbraith plot in figure 4 reports information about the study-specific effect sizes and there, precisions and shows the absence of potential outliers. The graph also provides information to assess heterogeneity among the effect sizes. The green reference line (y = 0) represents the "No effect" line. Most of the studies are above the reference line which indicates the effect size which is measured in terms of the correlation coefficient is higher than the rest. In the absence of substantial heterogeneity, it is expected that around 95% of correlation coefficient of the studies to lie within the 95% CI region (shaded area). Here in the above studies all lies within the shaded region and none of the studies are out of this area, that means there is no outlier indicating the decreased possibility of heterogeneity between studies included in this meta-analysis.

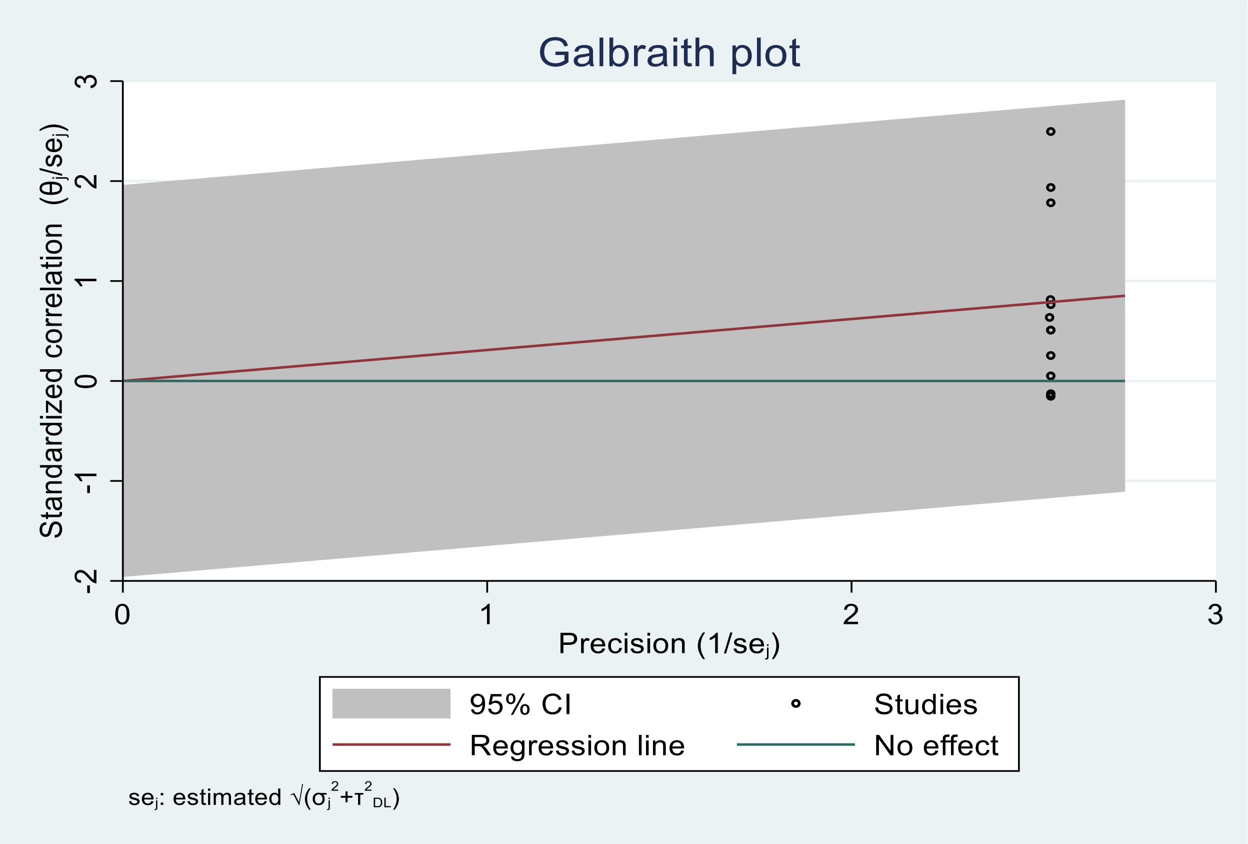


Fig. 4: *The heterogeneity test for studies that are conducted to show the association of FSH with HDL*

Publication Bias Assessment

Funnel Plot Analysis

As indicated in figure 5, the horizontal axis shows effect size which is the correlation coefficient, the vertical axis measures precision or standard error, the middle line in the funnel plot represents the overall calculated estimate of effect size. The blue dots indicate the effect of each individual study included in the metanalysis. There is no symmetry in the distribution of dots and most studies are scattered at the top.

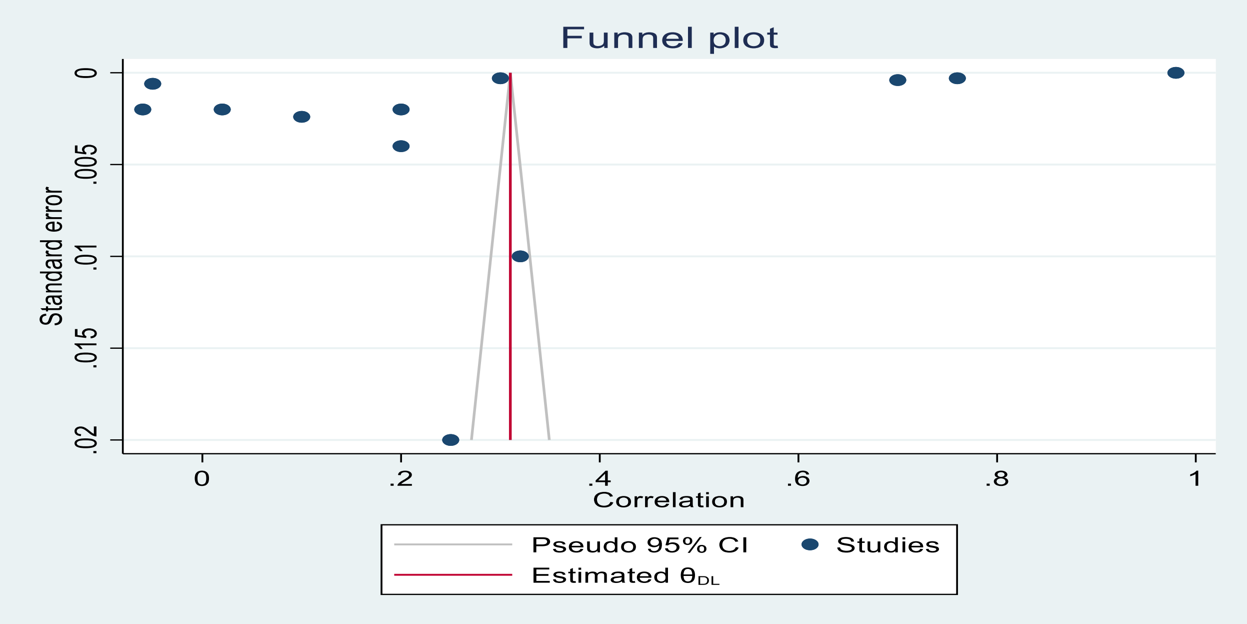
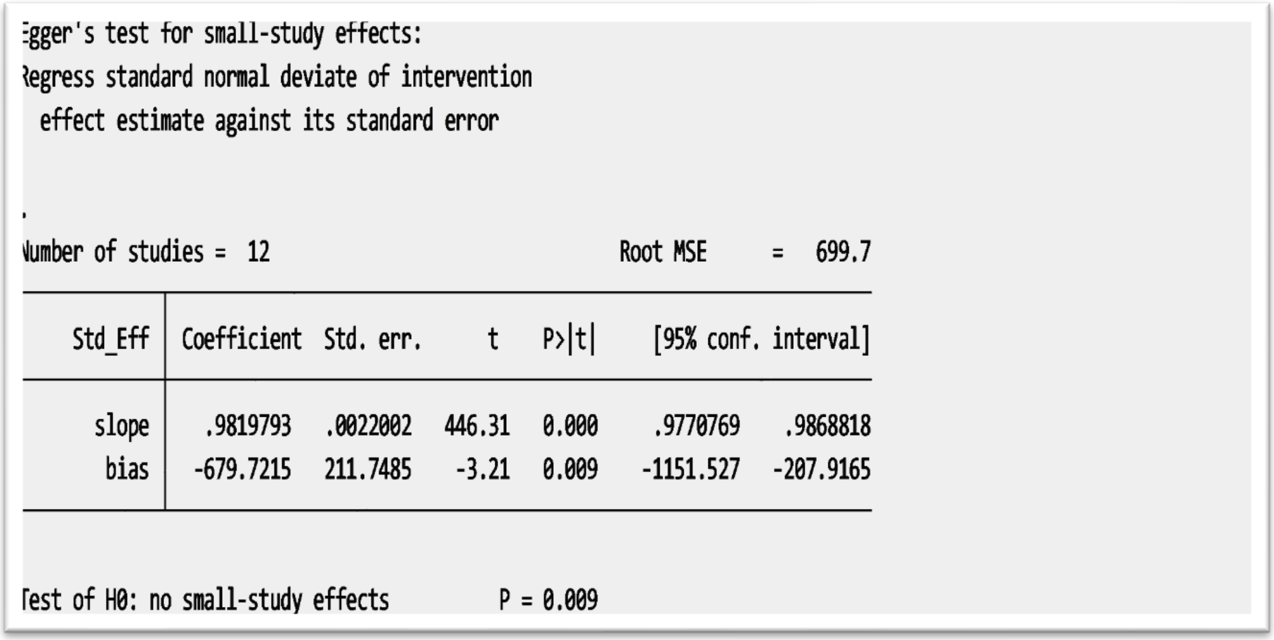


Fig. 5: *The diagram shows the publication bias check using funnel plot for graphical diagnostics of small study effects*

Egger's Test

The metric of interest here in the eggers test is the intercept line that is indicated by b. An intercept with a p-value< 0.05 is considered statistically significant and may indicate publication bias. In addition to this as the p-value is less than 0.1, there is evidence of asymmetry due to small study effects. As indicated in figure 6, small study effects using eggers test and the p-value shows significant possibility of publication bias p<0.05.



```
Egger's test for small-study effects:
Regress standard normal deviate of intervention
 effect estimate against its standard error

.
Number of studies =  12                    Root MSE      =   699.7
------------------------------------------------------------------
     Std_Eff | Coefficient  Std. err.      t    P>|t|     [95% conf. interval]
-------------+----------------------------------------------------
       slope |   .9819793   .0022002   446.31   0.000     .9770769    .9868818
        bias |  -679.7215   211.7485    -3.21   0.009    -1151.527   -207.9165
------------------------------------------------------------------

Test of H0: no small-study effects          P = 0.009
```

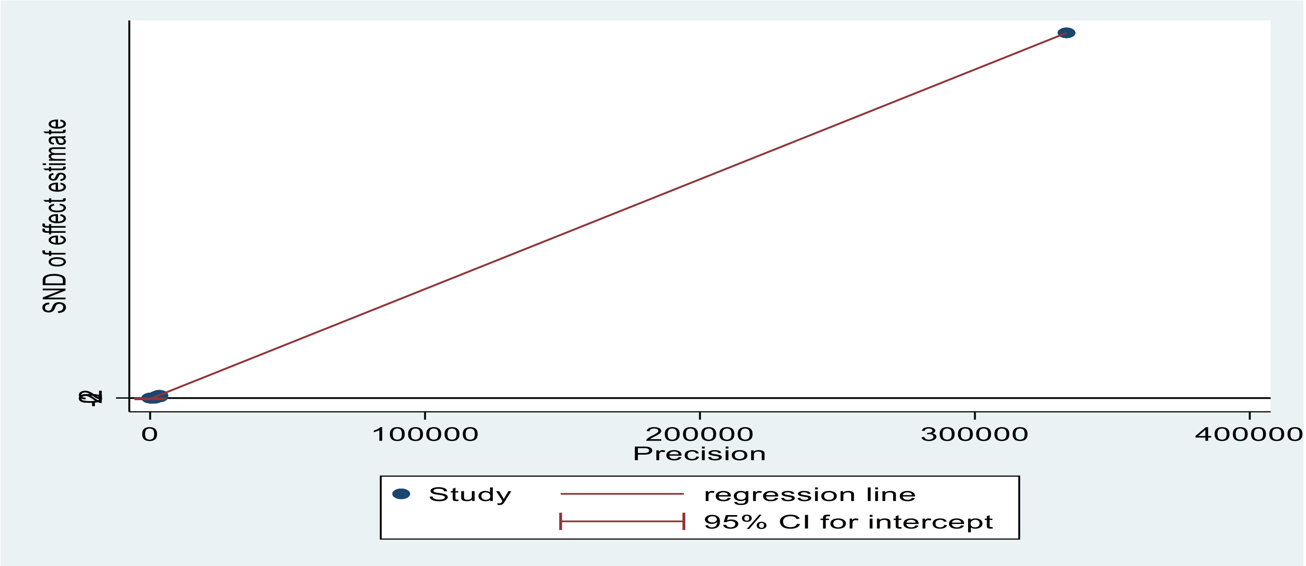
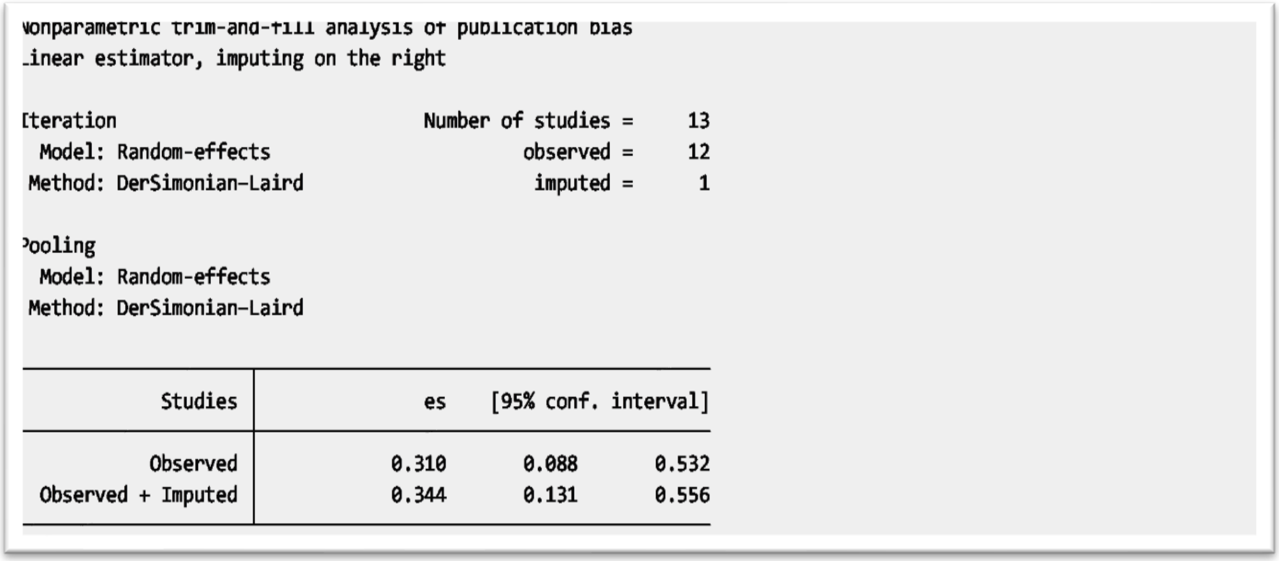


***Fig. 6**: Graphical presentation of publication bias using eggers test for HDL*

Trim and Fill Analysis

The above figure 7 is the funnel plot publication bias for trim and fill analysis shows that studies with statistically significant effect sizes are highly likely selected and published than studies with no significant effect sizes. There is unequal distribution of effect size. As the trim and fill analysis using a funnel plot produces effect sizes after trimming studies that produces overestimation for the pooled effect size, it produces the effect size after imputing studies but there is no substantial difference between the effect size of the original studies and effect size after trim and fill analysis implies that the small study effect is not most likely because of publication bias or the publication bias is minor and unlikely to significantly affect the overall correlation coefficient result. An adjusted estimate of the overall effect size which is the corrected correlation coefficient is 0.344. There is no larger difference between uncorrected correlation coefficient and recalculated one and no publication bias. Egger's test suggests small-study effects (asymmetry Figure 6), but trim-and-fill produced a similar pooled estimate, implying that while asymmetry exists, its impact on the pooled effect is likely small.



```
onparametric trim-and-fill analysis of publication bias
inear estimator, imputing on the right

teration                          Number of studies =     13
 Model: Random-effects                     observed =     12
Method: DerSimonian-Laird                  imputed =      1

ooling
 Model: Random-effects
Method: DerSimonian-Laird

------------------------------------------------------------
             Studies |          es    [95% conf. interval]
---------------------+--------------------------------------
            Observed |       0.310       0.088       0.532
 Observed + Imputed  |       0.344       0.131       0.556
------------------------------------------------------------
```

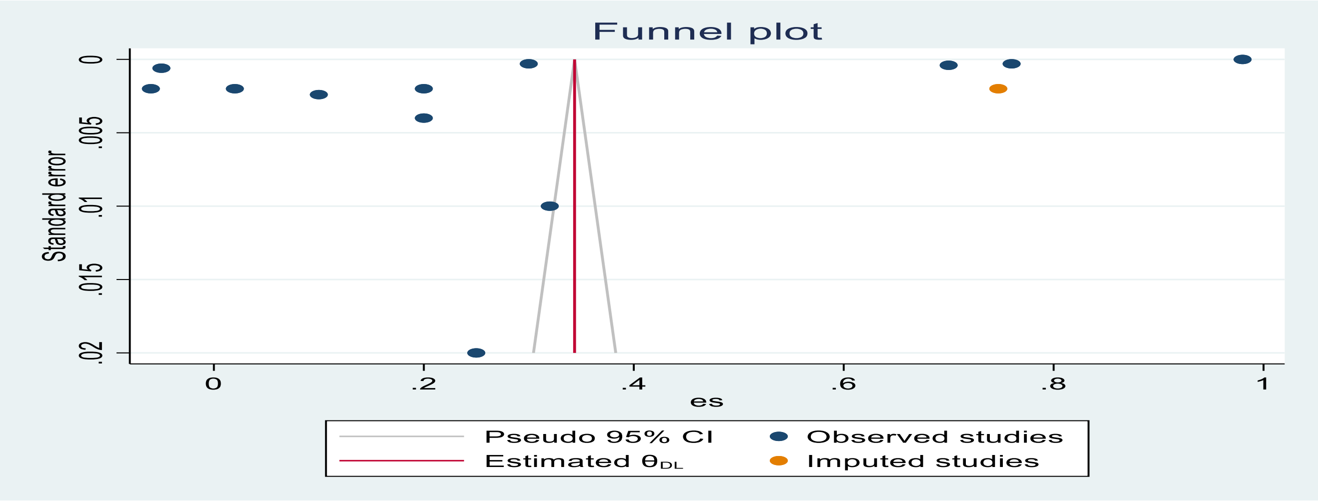
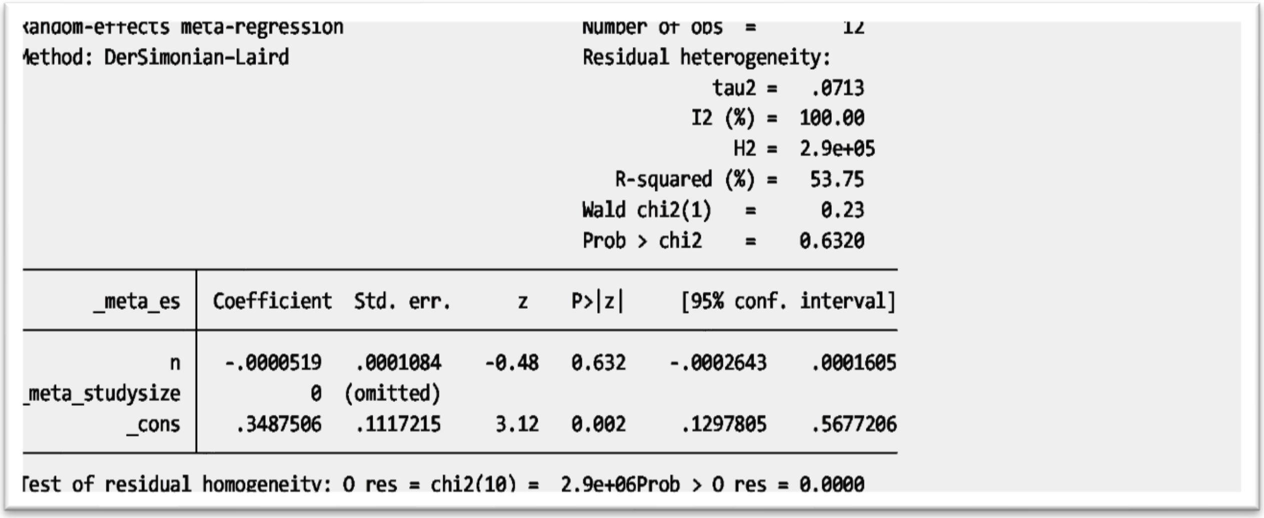


***Fig.** 7:Judgment of publication bias using Trim and fill analysis*

Meta Regression Analysis

The meta regression summary in table 2 , by considering sample size as a moderator shows the beta coefficient and the p-value having no statistical significance of sample size on the overall correlation coefficient which means the impact of sample size on the pooled correlation coefficient is not statistically significant indicating the presence of variability between studies included in this metanalysis, which means 100% of the variability in the residuals is still attributed to the between-study variation, there is no variability attributed to the within-study variation. In case of R2 which is used to assess proportion of between study variance, roughly 53% of the between-study variance is explained by the covariate sample size. The coefficient -0.00005, which means that everyone sample size increase corresponds to a decrease of 0.00005 units in the correlation coefficient. The test statistic Q-res is 2.9 with a p-value of 0.0000, which suggests the presence of heterogeneity among the residuals. As a conclusion, meta-regression using study size as a covariate indicated that this factor explained approximately 53.7% of the between-study heterogeneity ($R^2 = 53.7\%$). However, the regression slope was negligible (β = –0.00005; 95% CI: –0.00026 to 0.00016; P = 0.63), indicating no significant or clinically meaningful association between study size and effect size.

Table 2: Meta regression summary



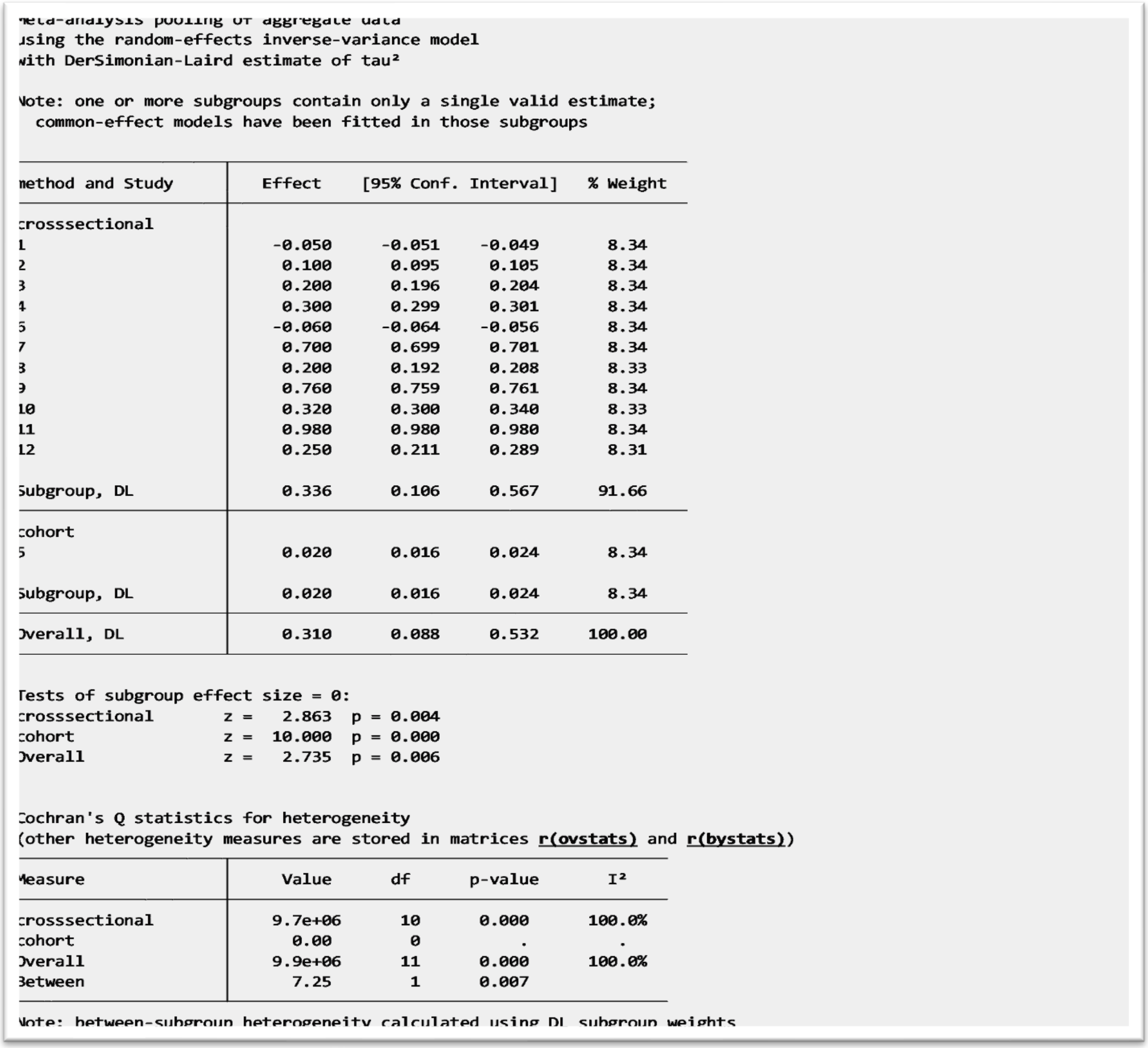
```
andom-effects meta-regression                    Number of obs  =         12
ethod: DerSimonian-Laird                         Residual heterogeneity:
                                                             tau2 =    .0713
                                                           I2 (%) =   100.00
                                                               H2 =  2.9e+05
                                                   R-squared (%) =    53.75
                                                 Wald chi2(1)   =      0.23
                                                 Prob > chi2    =    0.6320

        _meta_es | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
                 |
               n |  -.0000519   .0001084    -0.48   0.632    -.0002643    .0001605
 meta_studysize |          0  (omitted)
           _cons |   .3487506   .1117215     3.12   0.002     .1297805    .5677206

est of residual homogeneity: O res = chi2(10) =  2.9e+06Prob > O res = 0.0000
```

Subgroup Analysis

The overall effect size from the two study design methods was compared for the presence of significant difference between the effect sizes and the result in table 3 shows the presence of significant difference in the pooled correlation coefficient for the study designs. Subgroup analysis

showed a significant pooled effect among cross-sectional studies (θ = 0.34; 95% CI 0.19–0.57; P = 0.004), whereas the single cohort study showed no meaningful association (θ = 0.02; 95% CI 0.02–0.02). The difference between subgroups was statistically significant (Q = 7.25, P = 0.007), suggesting that study design contributed to heterogeneity. Substantial heterogeneity remained within the cross-sectional subgroup (I² = 100%)

*Table 3***: subgroup analysis summary**



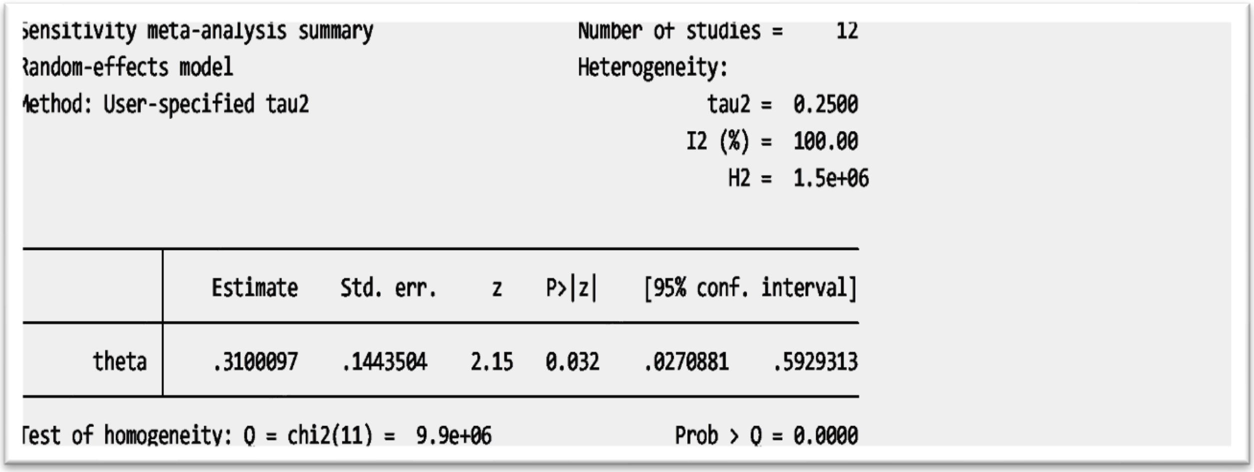
```
Meta-analysis pooling of aggregate data
using the random-effects inverse-variance model
with DerSimonian-Laird estimate of tau²

Note: one or more subgroups contain only a single valid estimate;
  common-effect models have been fitted in those subgroups

-----------------------------------------------------------------
method and Study      |   Effect    [95% Conf. Interval]   % Weight
----------------------+------------------------------------------
crosssectional        |
1                     |   -0.050     -0.051     -0.049       8.34
2                     |    0.100      0.095      0.105       8.34
3                     |    0.200      0.196      0.204       8.34
4                     |    0.300      0.299      0.301       8.34
5                     |   -0.060     -0.064     -0.056       8.34
7                     |    0.700      0.699      0.701       8.34
8                     |    0.200      0.192      0.208       8.33
9                     |    0.760      0.759      0.761       8.34
10                    |    0.320      0.300      0.340       8.33
11                    |    0.980      0.980      0.980       8.34
12                    |    0.250      0.211      0.289       8.31
                      |
Subgroup, DL          |    0.336      0.106      0.567      91.66
----------------------+------------------------------------------
cohort                |
6                     |    0.020      0.016      0.024       8.34
                      |
Subgroup, DL          |    0.020      0.016      0.024       8.34
----------------------+------------------------------------------
Overall, DL           |    0.310      0.088      0.532     100.00
-----------------------------------------------------------------

Tests of subgroup effect size = 0:
crosssectional       z =   2.863  p = 0.004
cohort               z =  10.000  p = 0.000
Overall              z =   2.735  p = 0.006


Cochran's Q statistics for heterogeneity
(other heterogeneity measures are stored in matrices r(ovstats) and r(bystats))
---------------------------------------------------------------
Measure               |     Value      df      p-value       I²
----------------------+----------------------------------------
crosssectional        |   9.7e+06      10      0.000     100.0%
cohort                |      0.00       0          .          .
Overall               |   9.9e+06      11      0.000     100.0%
Between               |      7.25       1      0.007
---------------------------------------------------------------
Note: between-subgroup heterogeneity calculated using DL subgroup weights
```

Sensitivity Analysis

To assess the robustness of the pooled estimates, we performed sensitivity analyses by comparing results obtained using both the random-effects model (DerSimonian–Laird) and the fixed-effect (inverse-variance) model. This allowed us to evaluate whether the choice of model substantially influenced the summary effect size or its precision. Additionally, we repeated the analysis after sequentially omitting one study at a time ('leave-one-out' analysis) to evaluate the influence of individual studies on the overall effect.

As indicated in table 4 which was done by replacing the Fixed Model with Random Model, the sensitivity analysis, conducted using a user-specified tau² in a random-effects model, yielded a pooled effect size of 0.31 (95% CI: 0.03–0.59; P = 0.03), which was consistent with the primary analysis. Despite a slightly larger between-study variance (tau² = 0.25), the effect remained significant, indicating that the findings are robust to changes in the variance estimator. However, heterogeneity remained extremely high (I² = 100%), suggesting considerable variability in study effects that is not resolved by altering the model

Table 4: The sensitivity analysis summary



```
ensitivity meta-analysis summary                 Number of studies =     12
andom-effects model                              Heterogeneity:
ethod: User-specified tau2                                   tau2 =  0.2500
                                                           I2 (%) =  100.00
                                                               H2 =  1.5e+06

                  |
                  |   Estimate   Std. err.      z    P>|z|     [95% conf. interval]
------------------+---------------------------------------------------------------
            theta |   .3100097    .1443504    2.15   0.032     .0270881    .5929313
------------------+---------------------------------------------------------------
est of homogeneity: Q = chi2(11) =  9.9e+06              Prob > Q = 0.0000
```

Discussion

In the present systematic review and meta-analysis the pooled calculated estimated correlation coefficient of FSH with HDL cholesterol was a moderate positive correlation(r = 0.31; 95% CI 0.09–0.53; p = 0.006). This correlation coefficient indicated a moderate positive association between the concentration of FSH and the level of HDL and the result was consistent with a crosssectional study conducted in china which had stated that lower FSH level was associated with lower HDL-C(Zhang et al., 2023). Moreover the result was consistent with another cohort study conducted in finland to show the association of FSH with cardiovascular risk factors among postmenopausal women and statistically significant ($p \leq 0.001$) correlation was observed between FSH and HDL levels(Bertone-Johnson et al., 2018). The result from this meta-analysis contradicted with the results from a cohort study conducted in Finland that had indicated an absence of significant relationship between the level of FSH with that of HDL(Serviente et al., 2019) and with a crosssectional study conducted in China that had shown the increase in serum FSH levels per 1 SD were negatively associated with reduced HDL(Chen et al., 2023). The possible reason for the discrepancy might be population difference as the studies are from china and finland that included different age groups of postmenopausal women ,adjustments for associated factors like BMI ,age and other sex hormones like estrogen and the nature of the study designs as causal relationships could not be determined by crosssectional studies as well as sample size difference as large sample size will give narrow confidence interval that will give good precesion(Azagew et al., 2024).

In the current meta-analysis, publication bias was checked by using Eggers test and Trimm and Fill Analysis. Egger's test suggests small-study effects (asymmetry), but trim-and-fill produced a similar pooled estimate, implying that while asymmetry exists, its impact on the pooled effect is likely small. The presence of high level of heterogeneity suggests that the included studies differ substantially in terms of factors such as study design, participant characteristics, measurement methods, or other confounding variables. Meta-regression using study size as a covariate indicated that this factor explained approximately 53.7% of the between-study heterogeneity ($R^2 = 53.7\%$). However, the regression slope was negligible ($\beta = –0.00005$; 95% CI: –0.00026 to 0.00016; $P = 0.63$), indicating no significant or clinically meaningful association between study size and effect size.

In subgroup analysis by considering study design as modifier for the overestimation of the pooled correlation coefficient, crosssectional studies had affected the results of the overall correlation coefficient relative to cohort.

Inorder to check the robustness of the pooled estimated correlation coefficient, sensitivity analyses was conducted by comparing results obtained using both the random-effects model (DerSimonian–Laird) and the fixed-effect (inverse-variance) model and the estimated pooled correlation coefficient was similar with the primary analysis. The effect remained significant, indicating that the findings are robust to changes in the variance estimator. However, heterogeneity remained extremely high ($I^2 = 100\%$), suggesting considerable variability in study effects that is not resolved by altering the model.

Implications of the study

The significant, unexplained variation in the correlation coefficient is the primary finding of this systematic review and analysis. The study emphasizes how follicle stimulating hormone affects postmenopausal women's HDL levels. The study's conclusions provide medical practitioners with recommendations on how to do routine lipid profile screening to reduce, identify, and manage the risk of potential problems during postmenopausal periods.

Limitations of the study

- The findings should be interpreted in light of several important constraints.
- The analysis showed extreme between-study heterogeneity ($I^2 = 100\ \%$), and the pooled estimate may therefore be unstable.
- Cross-sectional designs dominated (11 of 12 studies), limiting inference on causality.
- Residual confounding from unadjusted factors such as body-mass index, estrogen status, lifestyle behaviors and ethnicity cannot be excluded.
- Assay variability (differences in FSH platforms and sample handling) and restriction to English-language publications may have contributed to heterogeneity and potential language bias.
- Egger’s test indicated possible publication bias, although its impact on the pooled effect size was small.
- Together, these issues lower the overall certainty of the evidence to “low” despite the use of a comprehensive search strategy and robust statistical methods
- Standardized multiple regression tables were not considered because we cannot get a correlation coefficient from a single β without either the full predictor correlation matrix or additional regression statistics.
- Variation in assay kits and pre-analytical handling could contribute to measurement heterogeneity.
- We did not perform a formal GRADE assessment to rate the certainty of evidence for the pooled estimates

Conclusions

Significant positive correlation coefficient was observed betweeen the levels of FSH and HDL among studies that had included postmenopausal women as study participants and IPD meta-analysis or adequately adjusted prospective studies are recommended in the future.

Funding

The authors of this manuscript did not receive any funding

Availability of data and materials

The datasets used and/or analyzed for this study are available from the corresponding author upon reasonable request

Declarations

Clinical trial number: not applicable

Ethical Approval and consent to participate: not applicable
-Consent to Publication: not applicable
-Data Availability statement: not applicable
-Conflict of interest: The authors declare that they have no competing interests
-Acknowledgement: not applicable

References

Azagew, A. W., Abate, H. K., Mekonnen, C. K., Mekonnen, H. S., Tezera, Z. B., & Jember, G. (2024). Diabetic dyslipidemia and its predictors among people with diabetes in Ethiopia: Systematic review and meta-analysis. Systematic Reviews, 13(1), 190.

Bertone-Johnson, E. R., Virtanen, J. K., Niskanen, L., Nurmi, T., Ronkainen, K., Voutilainen, S., et al. (2017). Association of follicle-stimulating hormone levels and risk of type 2 diabetes in older postmenopausal women. Menopause, 24(7), 796–802.

Bertone-Johnson, E. R., Virtanen, J. K., Nurmi, T., Niskanen, L., Mursu, J., Voutilainen, S., et al. (2018). Follicle-stimulating hormone levels and subclinical atherosclerosis in older postmenopausal women. American Journal of Epidemiology, 187(1), 16–26.

Chen, Y., Wang, C., Sun, B., Wang, B., Lu, X., Gao, B., et al. (2023). Associations of follicle-stimulating hormone and luteinizing hormone with metabolic syndrome during the menopausal transition from the National Health and Nutrition Examination Survey. Frontiers in Endocrinology, 14, 1034934.

Chu, M. C., Rath, K. M., Huie, J., & Taylor, H. S. (2003). Elevated basal FSH in normal cycling women is associated with unfavourable lipid levels and increased cardiovascular risk. Human Reproduction, 18(8), 1570–1573.

El Khoudary, S. R., Wildman, R. P., Matthews, K., Thurston, R. C., Bromberger, J. T., & Sutton-Tyrrell, K. (2012). Endogenous sex hormones impact the progression of subclinical atherosclerosis in women during the menopausal transition. Atherosclerosis, 225(1), 180–186.

Herzog, R., Álvarez-Pasquin, M. J., Díaz, C., Del Barrio, J. L., Estrada, J. M., & Gil, Á. (2013). Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Public Health, 13, 1–17.

Litwak, S. A., Wilson, J. L., Chen, W., Garcia-Rudaz, C., Khaksari, M., Cowley, M. A., et al. (2014). Estradiol prevents fat accumulation and overcomes leptin resistance in female high-fat diet mice. Endocrinology, 155(11), 4447–4460.

Liu, X., Xu, J., Wei, D., & Chen, Y. (2023). Associations of serum follicle-stimulating hormone and luteinizing hormone levels with fat and lean mass during menopausal transition. Obesity Facts, 16(2), 184–193.

Mao, L., Wang, L., Bennett, S., Xu, J., & Zou, J. (2022). Effects of follicle-stimulating hormone on fat metabolism and cognitive impairment in women during menopause. Frontiers in Physiology, 13, 1043237.

Mauvais-Jarvis, F., Manson, J. E., Stevenson, J. C., & Fonseca, V. A. (2017). Menopausal hormone therapy and type 2 diabetes prevention: Evidence, mechanisms, and clinical implications. Endocrine Reviews, 38(3), 173–188.

Obeagu, E., & Obeagu, G. (2016). A review on haematological profile in menstruating, premenopausal and menopausal women. International Journal of Advanced Research in Biological Sciences, 3(11), 92–108.

Randolph, J. F., Jr., Zheng, H., Sowers, M. R., Crandall, C., Crawford, S., Gold, E. B., et al. (2011). Change in follicle-stimulating hormone and estradiol across the menopausal transition: Effect of age at the final menstrual period. The Journal of Clinical Endocrinology & Metabolism, 96(3), 746–754.

Serviente, C., Tuomainen, T.-P., Virtanen, J., Witkowski, S., Niskanen, L., & Bertone-Johnson, E. (2019). Follicle-stimulating hormone is associated with lipids in postmenopausal women. Menopause, 26(5), 540–545.

Song, Y., Wang, E.-S., Xing, L.-L., Shi, S., Qu, F., Zhang, D., et al. (2016). Follicle-stimulating hormone induces postmenopausal dyslipidemia through inhibiting hepatic cholesterol metabolism. The Journal of Clinical Endocrinology & Metabolism, 101(1), 254–263.

Wang, N., Shao, H., Chen, Y., Xia, F., Chi, C., Li, Q., et al. (2017). Follicle-stimulating hormone, its association with cardiometabolic risk factors, and 10-year risk of cardiovascular disease in postmenopausal women. Journal of the American Heart Association, 6(9), e005918.

Wenger, N. K. (2002). Clinical characteristics of coronary heart disease in women: Emphasis on gender differences. Cardiovascular Research, 53(3), 558–567.

Zhang, W., Chen, Y., Zhang, X., Chen, Y., Han, B., Li, Q., et al. (2023). Association of follicle-stimulating hormone with lipid profiles in older women: A cross-sectional SPECT-China study. BMJ Open, 13(7), e072796.